Mitochondrial dysfunction and decrease in body weight of transgenic knock-in mouse model for TDP-43: the question of glucose?

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LETTER

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Stribl *et al.* (1) observed 10% reduction in body weight and an altered lipid profile in a TDP-43 knock-in mouse model. These observations complement the emerging hypothesis that metabolic abnormalities are characteristic of TDP-43 proteinopathies, notably amyotrophic lateral sclerosis (ALS) (2). However, there are a number of inconsistencies in their observations and the data from ALS patients. Furthermore, we have some reservations about the interpretation of some of the data.

In the Summary and under "Discussion," Stribl *et al.* (1) mention that TDP-43 heterozygous mutants have an increase of glucose in the blood. However, Fig. 7 shows no difference in the level of blood glucose in either fasted or *ad libitum* fed mutant mice when compared with controls (1). Additionally, since pre-morbid diabetes mellitus delays the onset of ALS by 4 years (2), an increase in glucose is expected to be beneficial rather than detrimental in ALS models, an effect that has also been shown in TDP-43 *Caenorhabditis elegans* models (3). Further, Stribl *et al.* (1) demonstrate that the morphology and function of mitochondria are impaired in TDP-43 mutant mice. Hence, hypoglycemia rather than hyperglycemia is expected, because under mitochondrial impairment, the rate of glucose consumption through glycolysis is increased. Indeed, hypoglycemia is a feature of many mitochondrial disorders (4). One of the most probable reasons for increased blood glucose in TDP-43 knock-in mice is increased resistance to insulin, a feature of hypermetabolism observed in some ALS patients (5). To address this possibility, analyses of glucose and insulin tolerance would be essential.

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1. Stribl, C., Samara, A., Trümbach, D., Peis, R., Neumann, M., Fuchs, H., Gailus-Durner, V., Hrabě de Angelis, M., Rathkolb, B., Wolf, E., Beckers, J., Horsch, M., Neff, F., Kremmer, E., Koob, S., Reichert, A. S., Hans, W., Rozman, J., Klingenspor, M., Aichler, M., Walch, A. K., Becker, L., Klopstock, T., Glasl, L., Hölter, S. M., Wurst, W., and Floss, T. (2014) Mitochondrial dysfunction and decrease in body weight of a transgenic knock-in mouse model for TDP-43. *J. Biol. Chem.* **289,** 10769–10784
2. Jawaid, A., Paganoni, S., Hauser, C., and Schulz, P.E. (2014) Trials of antidiabetic drugs in amyotrophic lateral sclerosis: proceed with caution? *Neurodegener Dis.* **13,** 205–208
3. Tauffenberger, A., Vaccaro, A., Aulas, A., Vande Velde, C., and Parker, J. A. (2012) Glucose delays age-dependent proteotoxicity. *Aging Cell.* **11,** 856–866
4. Houten, S. M., and Wanders, R. J. (2010) A general introduction to the biochemistry of mitochondrial fatty acid β-oxidation. *J. Inherit. Metab. Dis.* **33,** 469–477
5. Dupuis, L., Pradat, P. F., Ludolph, A. C., and Loeffler, J. P. (2011) Energy metabolism in amyotrophic lateral sclerosis. *Lancet Neurol.* **10,** 75–82

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